December 25, 2015

Dear Editor,

On behalf of my co-authors, we thank you very much for giving us an opportunity to revise our manuscript, we appreciate you and all the reviewers very much for your positive and constructive comments and suggestions on our manuscript entitled" Pancreatic perivascular epithelioid cell tumor: A case report with clinicopathological feature and literature review". We have studied reviewers' comments carefully and have tried our best to revise our manuscript according to the comments. The revision which marked in the paper was highlighted in red. The main corrections in the paper and the responds to the reviewer's comments are as flowing:

Responds to the reviewer's comments:
Reviewer 1:
1.It is important that researchers indicate the name of the Ethics Committee approved the study and if the patient was treated according to the provisions of the Helsinki criteria to conduct research involving human subjects.

Response: The study was reviewed and approved by the Shanghai Changhai Hospital Ethnic Committee. The study was done after agreement with the patients' informed consent and the patient was treated according to the provisions of the Helsinki criteria.

2.In the introduction, it is recommended that the authors of this manuscript present in detail the epidemiological aspects of this type of tumor. Frequency by geographic location, sex, age, clinical manifestations and predisposing factors, if there is a hereditary predisposition, it would be appropriate to describe it.

Response: Epidemiological characteristics is of great importance for a disease. However, pancreatic perivascular epithelioid cell tumor is extremely rare and only thirteen cases including ours were reported during the last decade, the epidemiological features are not that clear. So, we did some analysis and chose to put them in the part of discussion. Combining these previous twelve cases with ours, we found that these patients with a mean age of 52 years (varied from 31 to 62 years) were mostly women, including eleven females and two males. Tuberous sclerosis (TSC) containing TSC1 or TSC2 gene deletion can be seen in some PEComas, especially in renal AKL. Nevertheless, all the PEComas of the pancreas presented without TSC. Abdominal pain is the main initial symptom in PEComa of the pancreas, while a few cases were asymptomatic that were found during health examination or follow-up examination for other disease. There is no explicit

predisposing factors or hereditary predisposition of this kind of disease.

3. What is the status of the patient clinical follow-up? , and what is the prognosis of the patients with this type of tumor?

Response: We followed up the patient though telephone for 14 months, no recurrence or distant metastases were observed. To date, the biological behavior and histologic origin of this kind of tumor were unknown. The pervasive concept is that PEComas are usually benign, whereas increasing reports indicated that PEComa may have malignant potential even though there is no consensus to evaluate the PEComa. In 2005, Folpe et al. put forward a diagnostic criteria of malignant PEComa, but it is difficult to confirm the accuracy of the criteria in distinguishing malignant PEComa from the benign one due to rare cases of PEComa of the pancreas. In these 13 cases, only one case can be regarded as malignant PEComa according to Folpe's criteria, in which liver metastasis occurred in 6 months after surgery. But this patient had a family history of breast cancer and BRCA2 gene mutation. The patient undertook radiotherapy and chemotherapy because of breast cancer 10 years ago. Therefore, whether malignant PEComa resulted from BRCA2 gene mutation or chemotherapy and radiotherapy was unknown. Additionally, another invasive PEComa cannot be diagnosed as malignant one, whereas multiple liver metastases were found in 27 months after surgery in this patient. Generally, more cases are required to be analyzed in order to evaluate the recurrent risk of PEComa.

4. What is the role of female sex hormones in the PEComas behavior?

Response: By analyzing these thirteen cases of pancreatic perivascular epithelioid cell tumor, we found that these patients were mostly women, including eleven females and two males. The morbidity of PEComa in female was significantly higher than that in male, suggesting that one risk factor of PEComa is related to sex hormone. Additionally, some studies revealed that progesterone receptors (PR) were expressed in PEComas immunohistochemically, especially in LAM and renal AKL. However, in these thirteen cases, PR was negatively expressed in five PEComas cases and only one PEComa partially expressed ER, so the role of female sex hormones in the PEComas of the pancreas behavior can`t be determined at the moment and it deserves further exploration.

5. It is recommended to present a conclusion of the case report.

Response: Thanks for your recommendation. In conclusion, as an unusual tumor deriving from mesenchyma, perivascular epithelioid cell tumor (PEComa) of the pancreas is always benign. Although most of the

reported cases are women, the role of female sex hormones in the PEComas of the pancreas behavior can`t be determined at the moment and it deserves further exploration. Cases such as concomitant with TSC or other syndromes have not been reported yet. Complete surgical resection is the main treatment for PEComa, whereas the necessity of resection and timing of surgical treatment are relatively limited. For liver metastasis may occur in some postoperative cases, we should closely follow up those with an invasive growth pattern, high mitotic index and large irregular shape of tumor cells. Further, for cases with huge inoperable tumor and multiple metastases, effective treatment is in lack since the effect of traditional radiotherapy and chemotherapy are poor. Until recently, Wagner et al. reported three cases of malignant PEComa reacted to mTOR inhibitor sirolimusin radiological examination, indicating that mTOR inhibitor may serve as a candidate for future targeted chemotherapy drug, but it also needs more cases of summary. As for benign PEComa, it is necessary to follow-up on a regular basis, but aggressive therapy is not suggested. And this conclusion has been changed in manuscript highlighted in red.

6. About the citations, the title of table and the explanations of contents of all figures.

Response: We are very sorry for our negligence, and we tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. And here we did not list the changes but marked in revised paper.

We appreciate for Editors/Reviewers' warm work earnestly, and hope that the correction will meet with approval.
Once again, thank you very much for your comments and suggestions.

Yours sincerely,

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